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(54) Title: PREPARATION OF HETEROARYL COMPOUNDS

(57) Abstract

This invention provides processes for the preparation of 4–heteroaryl–1,2,3,6–tetrahydropyridines and 4–heteroarylpiperidines.

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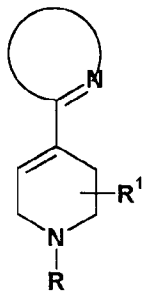
PREPARATION OF HETEROARYL COMPOUNDS

4-Arylpiperidines and 4-aryl-1,2,3,6-tetrahydropyridines as a class are known to exhibit diverse pharmacological activity. Piperidinylindoles and tetrahydropiperidinylindoles are known to be agonists at the serotonin 5-HT_1-like receptor (Baker et al., U.S. Patent #5,298,520), and to have affinity for the serotonin 5-HT_1, 5-HT_{1A}, and 5-HT_2 receptors (Taylor et al., Molecular Pharmacology, **34**, 42-53 (1988)). Certain piperidinylbenzothiophenes are known to be serotonin 5-HT_2 antagonists (Watanabe, et al., Journal of Heterocyclic Chemistry, **30**, 445 (1993)). Furthermore, certain 4-aryl-1,2,3,6-tetrahydropyridines and 4-arylpiperidines have been taught by Audia et al. (WO 97/47302) to be inhibitors of serotonin reuptake.

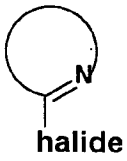
This class of molecules is generally accessed through coupling of an appropriate aryl substrate with a 4-piperidone or piperidone enolate derivative. Such coupling pairs include an aryl anion with a 4-piperidone; or an arylboronic acid with an enol triflate in the presence of a palladium catalyst. While these methods have provided access to a number of derivatives, those compounds where the point of connectivity to the heteroaryl moiety is adjacent to a nitrogen atom have been difficult or impossible to prepare. The present invention provides a process for the preparation of these heteroaryl-1,2,3,6-tetrahydropyridines and heteroarylpiperidines.

The present invention provides a process for the preparation of heteroaryl-1,2,3,6-tetrahydropyridines of Formula I:



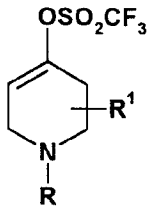
I

where R^1 is C_1-C_4 alkyl or a nitrogen protecting group; and R^2 is hydrogen or C_1-C_6 alkyl, comprising reacting a heteroaryl halide of Formula II:



II

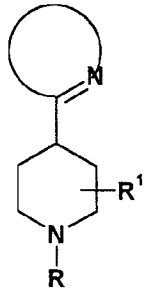
with a triflate of Formula III:



III

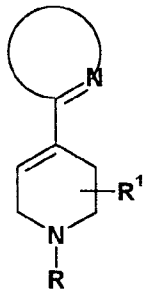
in the presence of a palladium catalyst, a hexa(C_1-C_6 alkyl)ditin, and lithium chloride in a suitable reaction medium.

The present invention also provides a process for the preparation of heteroarylpiperidines of Formula IV:



IV

comprising reducing the heteroaryl-1,2,3,6-tetrahydro-pyridines of Formula I:

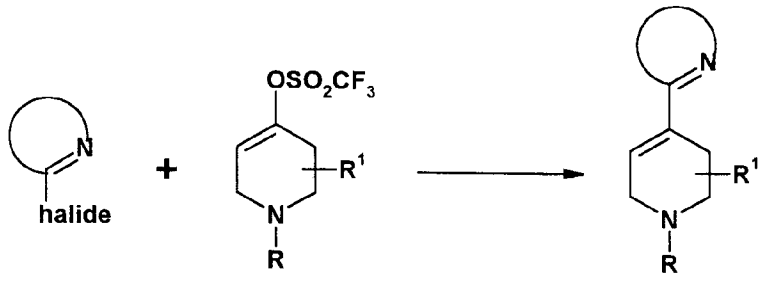


I

where R^1 is C_1-C_4 alkyl or a nitrogen protecting group and R^2 is hydrogen or C_1-C_6 alkyl.

The present invention also provides processes further comprising deprotecting those compounds of Formula I and Formula IV where R^1 is a nitrogen protecting group to provide the corresponding secondary amine.

This invention is useful for the transformation generically represented by the following equation:



II III I

where halide is chloro, bromo, or iodo; R^1 is C_1-C_4 alkyl or a nitrogen protecting group; and R^2 is hydrogen or C_1-C_6 alkyl. The process of the invention is performed by reacting an appropriate heteroaryl halide (II) with an appropriate triflate (III) in the presence of a palladium catalyst, a hexa(C_1-C_4 alkyl)ditin, and lithium chloride in a suitable solvent. Once the reaction is complete, the resultant tetrahydropyridine (I) is isolated by standard extractions and filtrations. If desired, the tetrahydropyridine product may be further purified by chromatography or crystallization as appropriate. While the order and manner of combining the reactants are not critical, and may be varied as a matter of convenience, it is preferred that the palladium catalyst is added last to the reaction mixture.

Reactions employing the process of the present invention are preferably performed at the reflux temperature of the chosen reaction medium. The reactions may be performed at temperatures below reflux if convenient or desired. The skilled artisan will appreciate that reaction rates typically decrease as the temperature is lowered.

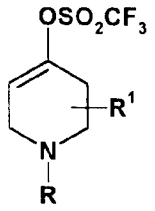
The heteroaryl portion of the heteroaryl halides (II) useful for the process of the present invention are characterized as a heterocyclic ring containing at least one sp^2-hybridized nitrogen atom which is adjacent to an sp^2-hybridized carbon atom bearing the halide atom. An sp^2-hybridized carbon atom is one that uses sp^2-hybridized

orbitals to form bonds with the three atoms to which it is attached. Likewise, an sp^2-hybridized nitrogen atom is one that uses sp^2-hybridized orbitals to form bonds with the two atoms to which it is attached. These sp^2-hybridized orbitals arise from hybridization of one 2s and two 2p electrons (March, Advanced Organic Chemistry, Third Edition (1985), pages 6-9, John Wiley and Sons, New York, NY).

The heterocyclic ring may be an isolated ring or it may be fused to other ring systems. The heterocyclic ring may also be substituted so long as the requisite functionality exists and the substituents do not interfere with the reaction. Heteroaryl moieties which are useful substrates for the process of the present invention include pyrazol-3-yl, imidazol-2-yl, imidazol-4-yl, pyridin-2-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-6-yl, pyridazin-3-yl, pyrazin-2-yl, indazol-3-yl, benzimidazol-2-yl, benzothiazol-2-yl, benzoxazol-2-yl, benzoisothiazol-3-yl, benzoisoxazol-3-yl, quinolin-2-yl, isoquinolin-1-yl, isoquinolin-3-yl, quinazolin-2-yl, quinazolin-4-yl, cinnolin-3-yl, phthalazin-1-yl, purin-2-yl, purin-6-yl, purin-8-yl, quinoxalin-2-yl, pteridin-2-yl, pteridin-4-yl, pteridin-6-yl, pteridin-7-yl, and the like.

The halide portion of the heteroaryl halide (II) is selected from chloro, bromo and iodo. Heteroaryl halides (II) where the halide is chloro are preferred. The heteroaryl halides (II) are either commercially available or may be prepared by techniques well known to one of ordinary skill in the art.

As previously stated, the triflate reagent is a compound of formula III:



III

where R^1 is C_1-C_4 alkyl or a nitrogen protecting group; and R^2 is hydrogen or C_1-C_6 alkyl. Nitrogen protecting groups are those moieties which allow the reactions of the process to proceed without interference by the secondary nitrogen atom, and then are subsequently removed to regenerate the secondary amine. Nitrogen protecting groups useful for the process of the invention are well known to the skilled artisan (Greene, Protective Groups in Organic Chemistry, Second Edition, Wiley Interscience, New York (1991)). Preferred protecting groups are phenoxycarbonyl and the C_1-C_4 alkoxycarbonyl groups, particularly tert-butoxycarbonyl. The requisite triflates are prepared by reacting the enolate of the corresponding piperidin-4-one with an appropriate triflating reagent, preferably N-phenyltrifluoromethanesulfonimide. The enolates may be prepared by treatment of the corresponding piperidin-4-one with a suitable base, or by conjugate addition of a nucleophilic reagent, such as a hydride reducing agent or a C_1-C_4 alkyl Grignard reagent, to the corresponding 1,2,3,4-tetrahydropyridin-4-one. These piperidin-4-ones and 1,2,3,4-tetrahydropyridin-4-ones are either commercially available or may be prepared by methods well known the skilled artisan.

The heteroaryl halide (II) and triflate (III) are typically added in about equimolar amounts, and this molar ratio is preferred. The skilled artisan will appreciate that a molar excess of either reagent relative to the other may be used if necessary or desired.

The palladium catalyst for the process of the present invention must be a palladium(0) catalyst such as tris(dibenzylideneacetone)dipalladium(0), tetrakis(triphenylphosphine)palladium(0), and tetrakis(methyldiphenylphosphine)-palladium(0). Where the palladium(0) catalyst is complexed to ligands, at least one or the ligands may be bound to an insoluble solid support if desired. Preferably, the palladium catalyst is tetrakis(triphenylphosphine)palladium(0). The palladium catalyst may be present in from about 2 to about 25 mole percent based on the amount of substrate. The amount of palladium catalyst ranging from about 5 to about 10 mole percent is preferred, and about 5 mole percent is most preferred for the process of the present invention.

The hexa(C_1-C_6 alkyl)ditin employed for the process of the present invention is not critical so long as at least about one molar equivalent of the reagent based on substrate is present. The preferred amount or ditin reagent is about an equimolar amount with substrate, and the preferred ditin reagent is hexamethylditin. The ditin reagents are either commercially available or may be conveniently prepared by methods well known to the skilled artisan.

The lithium chloride employed in the process of the present invention is used in excess relative to the substrates. From about a 2 to about a 10 fold molar excess of lithium chloride relative to substrate may be used. A molar excess of from about 2 to about five is preferred, with about a 3 fold molar excess being most preferred. The lithium chloride employed in the process of the present invention should be anhydrous. Anhydrous, as used here, is taken to mean that the lithium chloride is sufficiently free of water to facilitate the process of the present invention.

Reaction media useful for the process of the invention must be capable of dissolving a sufficient amount of the substrates for the process to proceed. Organic solvents useful as reaction media for the process of this invention

include ethers such as tetrahydrofuran, tetrahydropyran, dioxane, diethyl ether, diisopropyl ether, and methyl tert-butyl ether. The preferred solvent is dioxane. It is also preferred that the dioxane is anhydrous where anhydrous is taken to mean that the dioxane is sufficiently free of water to allow the process of the invention to proceed. It is also preferred that the reaction medium be deoxygenated prior to use in the process of the invention. Deoxygenation may be accomplished by bubbling an inert gas, such as nitrogen or argon, through the reaction medium. It is preferred that the reaction medium is deoxygenated with nitrogen.

The process may be carried out over a large range of concentrations, from about 0.05 molar to about 1 molar of he substrate, dependant upon the solubility of the particular substrate in the chosen reaction medium. The reaction may also be performed on slurries of the substrates so long as a sufficient amount of the substrate is soluble in the reaction medium for the reaction to proceed. Preferably the process is performed at a concentration from about 0.4 molar to about 1 molar. A concentration of about 0.4 molar to about 0.8 molar is most preferred.

The 1,2,3,6-tetrahydropyridines of Formula I where R^1 is a nitrogen protecting group are useful intermediates for the preparation of the corresponding secondary amines. The deprotection step may be accomplished by methods well known to the skilled artisan. The tert-butoxycarbonyl group, for example, may be removed by treatment with trifluoroacetic acid. The process of the present invention, therefore, further comprises deprotection of a compound of Formula I where R^1 is a nitrogen protecting group to provide the corresponding secondary amine.

The intermediate 1,2,3,6-tetrahydropyridines of Formula I may also be used to prepare the corresponding piperidines of Formula IV by hydrogenation over a precious metal catalyst, such as palladium on carbon. When the heteroaryl

moiety is substituted with a bromo group, a hydrogenation catalyst such as sulfided platinum on carbon, platinum oxide, or a mixed catalyst system of sulfided platinum on carbon with platinum oxide is used to prevent hydrogenolysis of the bromo substituent during reduction of the tetrahydropyridinyl double bond. The hydrogenation solvent may consist of a lower alkanol, such as methanol or ethanol, tetrahydrofuran, or a mixed solvent system of tetrahydrofuran and ethyl acetate. The hydrogenation may be performed at an initial hydrogen pressure of 20-80 p.s.i., preferably from 50-60 p.s.i., at 0-60°C, preferably at ambient temperature to 40°C, for 1 hour to 3 days. Additional charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate. The piperidines prepared in this manner are isolated by removal of the catalyst by filtration followed by concentration of the reaction solvent under reduced pressure. The product recovered may be used directly in a subsequent step or further purified by chromatography, or by recrystallization from a suitable solvent.

As an alternative to hydrogenation, 1,2,3,6-tetrahydropyridines may be converted to the corresponding piperidines by treatment with triethylsilane if desired. The 1,2,3,6-tetrahydropyridine is dissolved in trifluoroacetic acid to which is added an excess, 1.1-10.0 equivalents, of triethylsilane. The reaction mixture is stirred at about ambient temperature for from about 1 to about 48 hours at which time the reaction mixture is concentrated under reduced pressure. The residue is then treated with 2N sodium or potassium hydroxide and the mixture extracted with a water immiscible solvent such as dichloromethane or diethyl ether. The resultant piperidine may be purified by standard methods if necessary or desired. The resultant piperidine where R^1 is a nitrogen protecting group may then be removed as previously discussed to provide the

corresponding secondary amine. The skilled artisan will appreciate that the deprotection may occur prior or subsequent to the reduction of the double bond as necessary or desired. The present invention, therefore, also provides a process which further comprises the reduction of the 1,2,3,6-tetrahydropyridine double bond to prepare the corresponding piperidine and, where R^1 is a nitrogen protecting group, deprotecting the nitrogen.

The processes of the present invention are illustrated by the following Procedures and Examples, which are in no way intended to limit the scope of the present invention.

Preparation I

1-phenoxycarbonyl-2-methyl-1,2,3,4-tetrahydropiperidin-4-one

A solution of 1.5 gm (13.7 mMol) 4-methoxypyridine and 4.6 mL (13.7 mMol) methylmagnesium chloride in 30 mL tetrahydrofuran was cooled to -23°C at which time 1.72 mL (13.7 mMol) phenyl chloroformate was added. The reaction mixture was stirred for 20 minutes and was then poured into 10% hydrochloric acid and stirred for at room temperature for 10 minutes. This mixture was then extracted well with diethyl ether. The ether extracts were combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with 9:1 hexane:ethyl acetate. Fractions containing product were combined and concentrated under reduced pressure to provide 1.54 gm (49%) of the title compound as a white solid.

Preparation II

1,2-dimethylpiperidin-4-one

Ethyl 3-(N-methylamino)butanoate

A solution of 479.2 mL (0.958 mole) methylamine (2M in tetrahydrofuran) was added dropwise to 99.44 gm ethyl crotonate with stirring. After stirring 5 days at room

temperature the reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran. The residue was distilled to provide 91.25 gm (72%) of the desired product in 2 fractions.

MS(FD): m/e = 145 (M^+)

EA: Calculated for: $C_7H_{15}NO_2$: Theory: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.61; H, 10.66; N, 9.88.

Ethyl 3-(N-methyl-N-(2-ethoxycarbonyleth-1-yl)amino)butanoate

A mixture of 54.4 gm (0.374 mole) ethyl 3-(N-methyl-amino)butanoate and 100 gm (0.999 mole) ethyl acrylate was heated at 110°C with stirring for 18 hours. The reaction mixture was cooled to room temperature and then distilled under reduced pressure to provide 61.7 gm (67.1%) of the desired compound.

b.p.= 93-100°C (0.12 mm Hg)

MS(FD): m/e = 245 (M^+)

EA: Calculated for: $C_{12}H_{23}NO_4$: Theory: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.02; H, 9.65; N, 6.00.

Cyclization/decarboxylation

A solution of 43.0 gm (0.175 mole) ethyl 3-(N-methyl-N-(2-ethoxycarbonyleth-1-yl)amino)butanoate in 150 mL benzene was added dropwise to a stirring suspension of 5.6 gm (0.14 mole) sodium hydride (60% dispersion in mineral oil) in 100 mL benzene at room temperature. To this gelatinous mixture were added an additional 250 mL benzene and 3.5 gm (0.088 mole) sodium hydride (60% dispersion in mineral oil) and the mixture heated to reflux for 2 hours. The reaction mixture was then cooled to room temperature and acidified by the addition of concentrated hydrochloric acid. The phases were separated and the organic phase extracted with 3 x 100 mL 5N hydrochloric acid. The combined aqueous phases were allowed to stand at room temperature for 18 hours and were then heated to reflux for 4 hours. The reaction mixture was cooled to 0°C and basified (pH~14) with 50% aqueous NaOH. The mixture was extracted with 4 x 200 mL dichloromethane. The combined organic extracts were dried over sodium sulfate and then concentrated under reduced pressure to provide 22.2 gm of a brown oil. This residual oil was subjected to silica gel chromatography, eluting with 5% methanol in dichloromethane containing a trace of ammonium hydroxide. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 18.7 gm of an oil. This oil was fractionally distilled to provide 10.2 gm (46%) of the title compound.

MS(FD): m/e = 127 (M^+)

EA: Calculated for: $C_7H_{13}NO$: Theory: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.80; H, 10.44; N, 11.04.

Preparation III

1-tert-butoxycarbonyl-4-piperidone

A solution of 9.0 gm (61.5 mMol) 4-piperidone hydrochloride monohydrate in dioxane/water at 0°C was treated sequentially with aqueous sodium carbonate and 14.4 gm

(68 mMol) 2,2-dimethylpropanoic anhydride (BOC anhydride). The resultant slurry was stirred vigorously at room temperature for 18 hours. The reaction mixture was then concentrated under reduced pressure and the residue diluted with ethyl acetate. This mixture was treated with 1.5 M aqueous sodium hydrogen sulfate until the pH was about 2. The layers were separated and the remaining organics were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give 9.8 gm (80%) of the title compound as a tan solid.
EA: Calculated for: $C_{10}H_{17}NO_3$: Theory: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.54; N, 7.11.
MS(m/e): 199(M^+)

Preparation IV

1-phenoxycarbonyl-2-methyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine

A solution of 11.47 gm (49.8 mMol) 1-phenoxycarbonyl-2-methyl-1,2,3,4-tetrahydropiperidin-4-one in tetrahydrofuran was cooled to -23°C at which point 54.8 mL (54.8 mMol) L-Selectride (1.0 M in tetrahydrofuran) was added dropwise via an additional funnel. The reaction mixture was stirred for two hours and then a solution of 18.69 gm (52.3 mMol) N-phenyltrifluoromethanesulfonimide in tetrahydrofuran was added dropwise and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then concentrated under reduced pressure and the residue dissolved in diethyl ether. The ether extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with 9:1 hexane:ethyl acetate. Fractions containing product were combined and concentrated under reduced pressure to provide 9.46 gm (52%) of the title compound as a yellow oil.

EXAMPLE 1

4-(quinolin-2-yl)-1,2,3,6-tetrahydropyridine

1-tert-butoxycarbonyl-4-(quinolin-2-yl)-1,2,3,6-tetrahydropyridine

A mixture of 0.800 gm (4.9 mMol) 2-chloroquinoline, 1.62 gm (4.9 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 1.75 gm (4.9 mMol) hexamethylditin, 0.622 gm (14.7 mMol) anhydrous lithium chloride, and 0.283 gm (0.24 mMol) tetrakis(triphenylphosphine)palladium(0) in dioxane was stirred at reflux for about 16 hours. The reaction mixture was cooled to room temperature and then poured into saturated aqueous potassium fluoride. The mixture was then diluted with ethyl acetate and stirred for about 2 hours. The phases were separated and the organic phase washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with hexane containing about 6% ethyl acetate. Fractions containing product were combined and concentrated under reduced pressure to provide 0.632 gm of the desired compound as a light yellow oil.

Deprotection

A mixture of 0.632 gm (2.0 mMol) 1-tert-butoxycarbonyl-4-(quinolin-2-yl)-1,2,3,6-tetrahydropyridine, 5 mL trifluoroacetic acid, a drop of thiophenol, and 5 mL dichloromethane was stirred at room temperature for about 5 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and 2N sodium hydroxide. The phases were separated and the organic phase washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure to provide 0.268 gm (63%) of the title compound as a light yellow wax.

A portion was converted to the oxalate salt for analysis.

MS(FD): m/e = 210 (M^+)

EA: Calculated for $C_{14}H_{14}N_2$-$C_2H_2O_4$: Theory: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.13; H, 5.60; N, 9.57.

EXAMPLE 2

1-tert-butoxycarbonyl-4-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.52 gm (4.6 mMol) 2-chloropyridine and 1.53 gm (4.6 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyl-oxy-1,2,3,6-tetrahydropyridine, 0.59 gm (49%) of the title compound were prepared substantially by the procedure described in EXAMPLE 1.

EXAMPLE 3

1-tert-butoxycarbonyl-4-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.175 gm (1.5 mMol) 2-chloropyrimidine and 0.559 gm (1.7 mMol) 1-tert-butoxy-4-trifluoromethanesul-fonyloxy-1,2,3,6-tetrahydropyridine, 0.128 gm (32%) of the title compound were prepared as an off-white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 82-84°C

EA: Calculated for $C_{14}H_{19}N_3O_2$: Theory: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.53; H, 7.29; N, 16.23.

EXAMPLE 4

1-tert-butoxycarbonyl-4-(6-phenylpyridazin-3-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.226 gm (1.2 mMol) 6-phenyl-3-chloro-pyridazine and 0.413 gm (1.25 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.200 gm (50%) of the title compound were prepared as an off-white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 152-154°C

EA: Calculated for $C_{20}H_{23}N_3O_2$: Theory: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.27; H, 6.65; N, 12.39.

EXAMPLE 5

1-tert-butoxycarbonyl-4-(6-methoxyquinolin-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.250 gm (1.3 mMol) 2-chloro-6-methoxyquinoline and 0.472 gm (1.4 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.162 gm (37%) of the title compound were prepared as a waxy solid substantially by the procedure described in EXAMPLE 1.

m.p. = 85-87°C

EA: Calculated for $C_{20}H_{24}N_2O_3$: Theory: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.30; H, 7.22; N, 8.17.

EXAMPLE 6

1-tert-butoxycarbonyl-4-(benzimidazol-2-yl)-1,2,3,6-tetrahydropyridine 0.25 hydrate

Beginning with 0.203 gm (1.3 mMol) 2-chlorobenzimidazole and 0.466 gm (1.4 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.042 gm (11%) of the title compound were prepared as a waxy solid substantially by the procedure described in EXAMPLE 1.

m.p. = 215-216°C

EA: Calculated for $C_{17}H_{21}N_3O_2$-0.25 H_2O: Theory: C, 67.19; H, 7.13; N, 13.83. Found: C, 66.85; H, 7.13; N, 13.24.

EXAMPLE 7

1-tert-butoxycarbonyl-4-(1-tert-butoxycarbonylbenzimidazol-2-yl)-1,2,3,6-tetrahydropyridine 0.25 hydrate

Beginning with 0.380 gm (1.5 mMol) 1-tert-butoxycarbonyl-2-chlorobenzimidazole and 0.524 gm (1.6 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.159 gm (27%) of the title compound were prepared substantially by the procedure described in EXAMPLE 1.

m.p. = 92-93°C

EA: Calculated for $C_{22}H_{29}N_3O_4$-0.25 H_2O: Theory: C, 65.41; H, 7.36; N, 10.40. Found: C, 65.49; H, 7.24; N, 10.96.

EXAMPLE 8

1-tert-butoxycarbonyl-4-(quinoxalin-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.264 gm (1.6 mMol) 2-chloroquinoxaline and 0.587 gm (1.8 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.369 gm (74%) of the title compound were prepared as a light orange waxy solid substantially by the procedure described in EXAMPLE 1.

m.p. = 93-95°C

EA: Calculated for $C_{18}H_{21}N_3O_2$: Theory: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.57; H, 6.74; N, 13.56.

EXAMPLE 9

1-tert-butoxycarbonyl-4-(benzoxazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.204 gm (1.3 mMol) 2-chlorobenzoxazole and 0.487 gm (1.47 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.196 gm (49%) of the title compound were prepared as a white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 129-132°C

EA: Calculated for $C_{17}H_{20}N_3O_3$: Theory: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.79; H, 6.70; N, 9.62.

EXAMPLE 10

1-tert-butoxycarbonyl-4-(benzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.214 gm (1.3 mMol) 2-chlorobenzothiazole and 0.462 gm (1.39 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.232 gm (58%) of

the title compound were prepared as an off-white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 105-107°C

EA: Calculated for $C_{17}H_{20}N_3O_2S$: Theory: C, 64.53; H, 6.37; N, 8.85. Found: C, 64.37; H, 6.24; N, 8.67.

EXAMPLE 11

4-(4-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

1-tert-butoxycarbonyl-4-(4-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 2.0 gm (10 mMol) 2,4-dichlorobenzothiazole and 3.58 gm (10.8 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 2.16 gm (63%) of the desired compound were prepared as a light yellow waxy solid substantially by the procedure described in EXAMPLE 1.

m.p. = 98-101°C

EA: Calculated for $C_{17}H_{19}N_2O_2SCl$: Theory: C, 58.20; H, 5.46; N, 7.98. Found: C, 58.43; H, 5.55; N, 8.01.

Deprotection

Beginning with 0.805 gm (2.3 mMol) 1-tert-butoxycarbonyl-4-(4-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine, 0.497 gm (86%) of the title compound were prepared as an off-white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 112-114°C

MS(FD): m/e = 250 (M^+)

EA: Calculated for $C_{12}H_{11}N_2SCl$: Theory: C, 57.48; H, 4.42; N, 11.17. Found: C, 57.78; H, 4.48; N, 11.04.

EXAMPLE 12

4-(6-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

1-tert-butoxycarbonyl-4-(6-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 2.0 gm (10 mMol) 2,6-dichlorobenzothiazole and 3.91 gm (11.8 mMol) 1-tert-butoxy-4-trifluorometh-

anesulfonyloxy-1,2,3,6-tetrahydropyridine, 1.77 gm (51%) of the desired compound were prepared as a waxy solid substantially by the procedure described in EXAMPLE 1.

EA: Calculated for $C_{17}H_{19}N_2O_2SCl$: Theory: C, 58.20; H, 5.46; N, 7.98. Found: C, 57.90; H, 5.48; N, 8.01.

Deprotection

Beginning with 0.408 gm (1.2 mMol) 1-tert-butoxycarbonyl-4-(6-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine, 0.158 gm (54%) of the title compound were prepared as an off-white solid substantially by the procedure described in EXAMPLE 1.

m.p. = 125°C

MS(FD): m/e = 250 (M^+)

EA: Calculated for $C_{12}H_{11}N_2SCl$: Theory: C, 57.48; H, 4.42; N, 11.17. Found: C, 57.19; H, 4.63; N, 11.01.

EXAMPLE 13

1-tert-butoxycarbonyl-4-(4-methylbenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.227 gm (1.2 mMol) 2-chloro-4-methyl-benzothiazole and 0.409 gm (1.3 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.254 gm (64%) of the title compound were prepared as an off-white waxy solid substantially by the procedure described in EXAMPLE 1.

EA: Calculated for $C_{18}H_{22}N_2O_2S$: Theory: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.68; H, 6.57; N, 8.57.

EXAMPLE 14

1-tert-butoxycarbonyl-4-(4-methoxybenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.231 gm (1.2 mMol) 2-chloro-4-methoxy-benzothiazole and 0.403 gm (1.2 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.191 gm (48%) of the title compound were prepared as an

off-white solid substantially by the procedure described in EXAMPLE 1.

EA: Calculated for $C_{18}H_{22}N_2O_3S$: Theory: C, 62.40; H, 6.40; N, 8.09. Found: C, 62.23; H, 6.25; N, 8.06.

EXAMPLE 15

1-tert-butoxycarbonyl-4-(5-nitrobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine hemihydrate

Beginning with 0.130 gm (0.6 mMol) 2-chloro-5-nitrobenzothiazole and 0.211 gm (0.64 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.031 gm (14%) of the title compound were prepared as a light yellow waxy solid substantially by the procedure described in EXAMPLE 1.

EA: Calculated for $C_{17}H_{19}N_3O_4S$-0.5 H_2O: Theory: C, 55.12; H, 5.44; N, 11.34. Found: C, 55.36; H, 5.31; N, 11.07.

EXAMPLE 16

1-tert-butoxycarbonyl-4-(purin-6-yl)-1,2,3,6-tetrahydropyridine

Beginning with 0.256 gm (1.7 mMol) 6-chloropurine and 0.579 gm (1.7 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.097 gm (21% based on recovered starting material) of the title compound were prepared as a light tan foam substantially by the procedure described in EXAMPLE 1.

m.p. = 84°C

EA: Calculated for $C_{15}H_{19}N_5O_2$: Theory: C, 59.79; H, 6.35; N, 23.24. Found: C, 59.54; H, 6.30; N, 23.41.

EXAMPLE 17

4-(6-chlorobenzothiazol-2-yl)piperidine

1-tert-butoxycarbonyl-4-(6-chlorobenzothiazol-2-yl)piperidine

A mixture of 0.939 gm (2.7 mMol) 1-tert-butoxycarbonyl-4-(6-chlorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine and a catalytic amount of platinum oxide in 20 mL methanol was stirred at room temperature under about 1 atmosphere of hydrogen for about 3 hours. The reaction mixture was concentrated under reduced pressure and the residue dissolved in a minimal volume of ethyl acetate. This mixture was passed through a bed of silica gel, eluting with a 1:1 mixture of ethyl acetate and hexane. The filtrate was concentrated underreduced pressure to provide 0.663 gm (70%) of the desired compound as a light tan oil.

Deprotection

Beginning with 0.663 gm (1.9 mMol) 1-tert-butoxy-carbonyl-4-(6-chlorobenzothiazol-2-yl)piperidine, 0.263 gm (55%) of the title compound were recovered as an off-white solid substantially by the procedure described in EXAMPLE 14.

m.p. = 115-117°C

MS(FD): m/e = 252 (M^+)

EXAMPLE 18

1-tert-butoxycarbonyl-2-methyl-4-(4,5-dimethylbenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 1.30 gm (6.58 mMol) 2-chloro-4,5-dimethylbenzothiazole and 2.28 gm (6.58 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 1.0 gm (43%) of the title compound were prepared as an oily semi-solid, substantially by the procedure described in EXAMPLE 1.

MS(ion spray): m/e = 360.5 (M^+)

EXAMPLE 19

1-tert-butoxycarbonyl-2-methyl-4-(5,6-dimethylbenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 1.00 gm (5.06 mMol) 2-chloro-5,6-dimethylbenzothiazole and 1.74 gm (5.06 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 0.89 gm (49%) of the title compound were prepared as an oily semi-solid, substantially by the procedure described in EXAMPLE 1.

MS(ion spray): m/e = 360.5 (M^+)

EXAMPLE 20

1-tert-butoxycarbonyl-2-methyl-4-(4,6-difluorobenzothiazol-2-yl)-1,2,3,6-tetrahydropyridine

Beginning with 1.50 gm (7.30 mMol) 2-chloro-4,6-difluorobenzothiazole and 2.52 gm (7.30 mMol) 1-tert-butoxy-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine, 1.49 gm (56%) of the title compound were prepared as an oily semi-solid, substantially by the procedure described in EXAMPLE 1.

MS(ion spray): m/e = 366 (M^+)

Compounds available by the process of the present invention are useful intermediates for the preparation of pharmacologically active compounds. Certain of the compounds available by the process of the present invention are inhibitors of serotonin reuptake. The efficacy of compounds to inhibit the reuptake of serotonin has been determined by a paroxetine binding essay, the usefulness of which is set out by Wong, et al., Neuropsychopharmacology, 8, 23-33 (1993). Synaptosomal preparations from rat cerebral cortex were made from the brains of 100-150 g Sprague-Dawley rats which were killed by decapitation. The cerebral cortex was homogenized in 9 volumes of a medium containing 0.32 M sucrose and 20 μM glucose. The preparations were resuspended after centrifugation by homogenizing in 50 volumes of cold reaction medium (50 μM sodium chloride, 50 μM potassium chloride, pH 7.4) and

centrifuging at 50,000 g for 10 minutes. The process was repeated two times with a 10-minute incubation at 37°C between the second and third washes. The resulting pellet was stored at -70°C until use. Binding of ^{3}H-paroxetine to 5-HT uptake sites was carried out in 2 ml reaction medium containing the appropriate drug concentration, 0.1 nM ^{3}H-paroxetine, and the cerebral cortical membrane (50 μg protein/tube). Samples were incubated at 37°C for 30 minutes; those containing 1 μM fluoxetine were used to determine nonspecific binding of ^{3}H-paroxetine. After incubation, the tubes were filtered through Whatman GF/B filters, which were soaked in 0.05% polyethylenimine for 1 hour before use, using a cell harvester by adding about 4 ml cold Tris buffer (pH 7.4), aspirating, and rinsing the tubes three additional times. Filters were then placed in scintillation vials containing 10 ml scintillation fluid, and the radioactivity was measured by liquid scintillation spectrophotometry.

Certain compounds available by the method of the present invention have been tested in this assay and have been found to be inhibitors of serotonin reuptake. The compound of Example 12 was found to have a K_i of 20.9 nMol.

The pharmacological activities which have been described immediately above provide the mechanistic basis for the pharmaceutical utility of the compounds available by the process of the present invention. A number of pharmaceutical utilities will be described below.

It is now known that numerous physiological and therapeutic benefits are obtained through the administration of drugs which inhibit the reuptake of serotonin. The treatment of depression with drugs of the class of which fluoxetine is the leader has become perhaps the greatest medical breakthrough of the past decade. Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now

recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the human population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine was a breakthrough in the treatment of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago. Duloxetine is in clinical trials for the treatment of depression and is likely to become a marketed drug for the purpose.

Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids. Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke. Depression in all its variations is a preferred target of treatment with the present adjunctive therapy method and compositions.

Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the victim's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond any rational need or rationale, are the outward characteristic of the disease. A badly afflicted subject may be unable to do anything but carry out the rituals required by the disease. Fluoxetine is approved in the United States and other countries for the treatment of obsessive-compulsive disease and has been found to be effective.

Obesity is a frequent condition in the American population. It has been found that fluoxetine will enable an obese subject to lose weight, with the resulting benefit

to the circulation and heart condition, as well as general well being and energy.

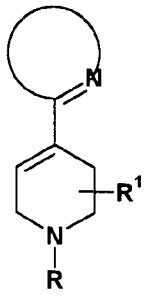
In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00
migraine
pain, particularly neuropathic pain
bulimia, ICD 307.51, DSM 307.51
premenstrual syndrome or late luteal phase syndrome, DSM 307.90
alcoholism, ICD 305.0, DSM 305.00 & 303.90
tobacco abuse, ICD 305.1, DSM 305.10 & 292.00
panic disorder, ICD 300.01, DSM 300.01 & 300.21
anxiety, ICD 300.02, DSM 300.00
post-traumatic syndrome, DSM 309.89
memory loss, DSM 294.00
dementia of aging, ICD 290
social phobia, ICD 300.23, DSM 300.23
attention deficit hyperactivity disorder, ICD 314.0
disruptive behavior disorders, ICD 312
impulse control disorders, ICD 312, DSM 312.39 & 312.34
borderline personality disorder, ICD 301.83, DSM 301.83
chronic fatigue syndrome
premature ejaculation, DSM 302.75
erectile difficulty, DSM 302.72
anorexia nervosa, ICD 307.1, DSM 307.10
disorders of sleep, ICD 307.4
autism
mutism
trichotillomania

CLAIMS

We claim:

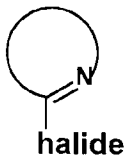
1. A process for the preparation of heteroaryl-1,2,3,6-tetrahydropyridines of Formula I:



I

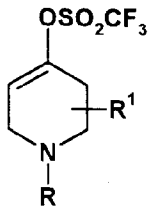
where:

R^1 is C_1-C_4 alkyl or a nitrogen protecting group and R^2 is hydrogen or C_1-C_6 alkyl, comprising reacting a heteroaryl halide of Formula II:



II

where halide is chloro, bromo, or iodo, with a triflate of Formula III:

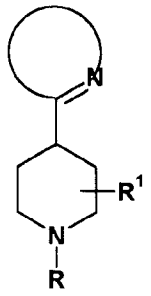


III

in the presence of a palladium catalyst, a hexa(C_1-C_6 alkyl)ditin, and lithium chloride in a suitable reaction medium.

2. A process of Claim 1, where halide is chloro.

3. A process of either of Claims 1 or 2, further comprising reducing the heteroaryl-1,2,3,6-tetrahydropyridine of Formula I to prepare a heteroarylpiperidine of Formula IV:



IV.

4. A process of any of Claims 1-3, where R^1 is a nitrogen protecting group, further comprising removal of the nitrogen protecting group.

5. A process of any of Claims 1-4, where the palladium catalyst is tetrakis(triphenylphosphine)-palladium(0).

6. A process of any of Claims 1-5, where the hexa(C_1-C_6 alkyl)ditin is hexamethylditin.

7. A process of any of Claims 1-6, where the suitable reaction medium is dioxane.

8. A process of any of Claims 1-7, where R^1 is a nitrogen protecting group.

9. A process of Claim 8, where the nitrogen protecting group is tert-butoxycarbonyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13521

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 401.04
US CL :546/167, 260, 153, 273.4, 271.7, 270.1; 544/333, 238, 284, 264
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/167, 260, 153, 273.4, 271.7, 270.1; 544/333, 238, 284, 264

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WUSTROW et al. Coupling of arylboronic Acid with a partially Reduced pyridine Derivative. Synthesis. November 1991, No. 11, pages 993-995.	1-2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 AUGUST 1999	Date of mailing of the international search report 10 SEP 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE FAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13521

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 3-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.